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Activation of Hydrogen Peroxide by Diphenyl Diselenide for Highly Enantioselective Oxaziridinium Salt-Mediated Catalytic Asymmetric Epoxidation

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Abstract: The first reported use of benzeneperseleninic acid as a catalytic mediator for oxaziridinium ion catalysed epoxidation is described, providing reaction rates and ees (up to 85%) similar to those reported when using oxone as the stoicheiometric oxidant. A dual catalytic cycle is proposed, in which diphenydiselenide is initially converted into the perseleninic acid, which in turn oxidizes an iminium ion to the corresponding oxaziridium species, thus facilitating asymmetric oxygen transfer to an alkene.

Key words: Epoxidation, Iminium salt, Oxaziridinium, Diphenyldiselenide, Oxidation.

Oxaziridinium salts have emerged as highly active species for the asymmetric epoxidation of unfunctionalized alkenes. We[1] and others[2] have reported a range of exo- and endo- cyclic iminium salt pre-catalysts that when treated with oxone undergo oxidation to the corresponding oxaziridinium salts, which are then able to transfer oxygen to alkenes (Scheme 1).
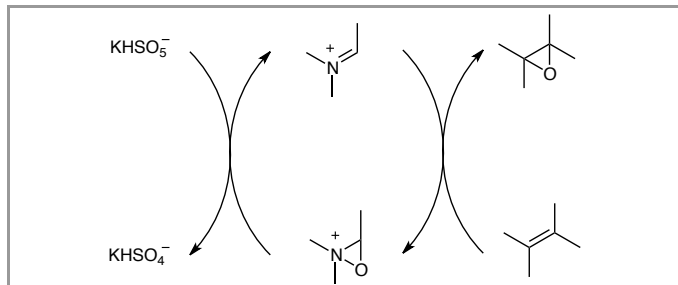
Scheme 1: General catalytic cycle involving oxaziridinium salts

The standard conditions employed in asymmetric epoxidation reactions catalysed by oxaziridinium salts involve the use of oxone as stoicheiometric oxidant, a base (typically 2 molar equivalents of Na_2CO_3 per equivalent of oxone), and water/acetonitrile as solvent mixture (Scheme 2):[3] the presence of water is essential for oxone solubility. Under the reaction conditions, there are separate aqueous and organic phases; it is possible that the catalyst acts as a phase transfer agent under these reactions.
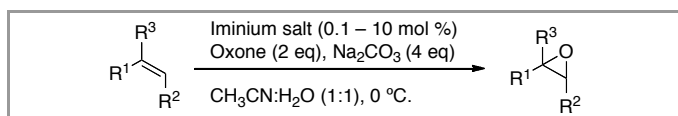

Scheme 2: The standard conditions applied for catalytic asymmetric epoxidation mediated by oxone and iminium salts.

The principal limitation to this system is the restricted range of temperatures at which the epoxidation can be per-formed (a little below 0 ºC to room temperature). The upper limit is determined by the oxone, which decomposes relatively quickly in the basic medium at room temperature.[4] The lower limit is determined by the use of the aqueous medium; one typical ratio of the water and acetonitrile co-solvents used is 1:1, and this mixture freezes at around –8 ºC.

One potential opportunity to enhance the enantioselectivity of the oxidation process would be provided if the reaction could be carried out at lower temperatures. This would require the development of non-aqueous reaction conditions, and, because of the solubility profile of oxone, which has no significant solubility in any organic solvent, this in turn dictates a need for a new stoicheiometric oxidant, soluble in organic solvents at low temperatures. Crucially, this oxidant must not itself oxidize alkenes under the reaction conditions in the absence of the catalyst (background, non-enantioselective, oxidation).

Towards this end we have reported the use of tetraphenylphosphonium monoperoxysulfate (TPPP) (originally reported by Di Furia in 1994 for oxygen transfer to manganese porphyrins),[5] which has proved to be an excellent oxidant for highly enantioselective epoxidations.[6] For example, epoxidation of *cis*-alkene **1** affords the corresponding epoxide **2** with 97% ee when employing iminium salt **3** (Scheme 3).[7] This system has since been used for the highly enantioselective total syntheses of levcromakalim [(–)-cromakalim],[7] (−)-(3'*S*)-lomatin,[8] (+)-(3'S,4'R)-*trans*-khellactone,[8] and (+)-scuteflorin[9] (Figure 1).
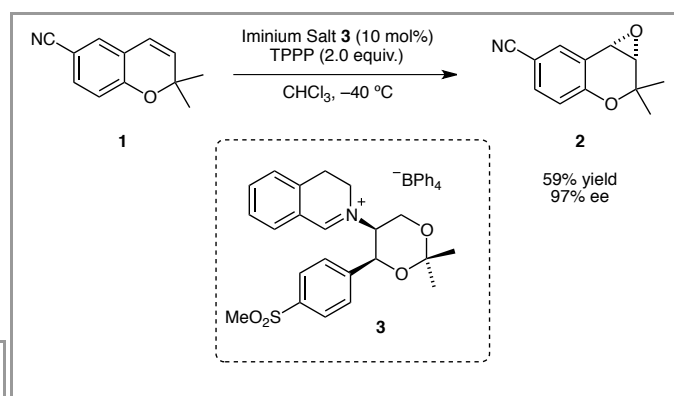
Scheme 3: Highly enantioselective epoxidation of *cis*- alkenes such as **1** mediated by iminium salt **3**.

We have also reported the use of hydrogen peroxide-[10] and sodium hypochlorite-[11] driven systems for asymmetric oxaziridinium salt-mediated epoxidation.
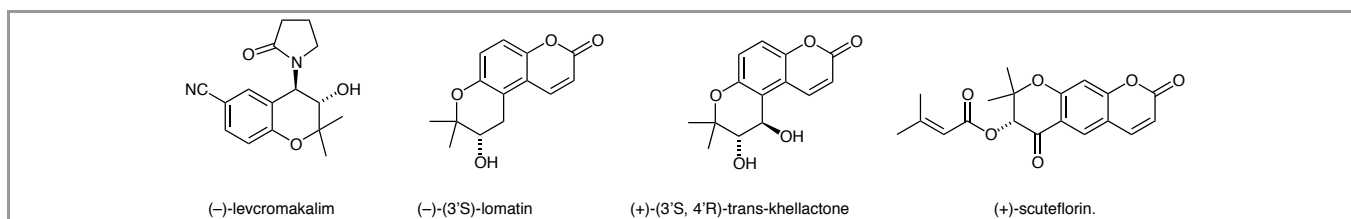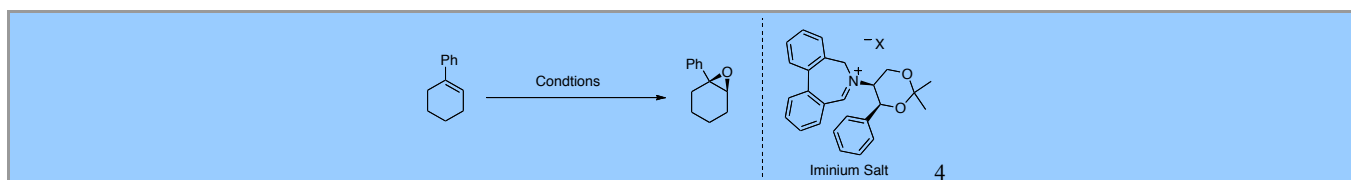
(−)-levcromakalim   (−)-(3'S)-lomatin   (+)-(3'S, 4'R)-trans-khellactone   (+)-scuteflorin.

Figure 1

Table 1   A comparison of epoxidation conditions for 1-phenylcyclohexene and iminium salt **4**.

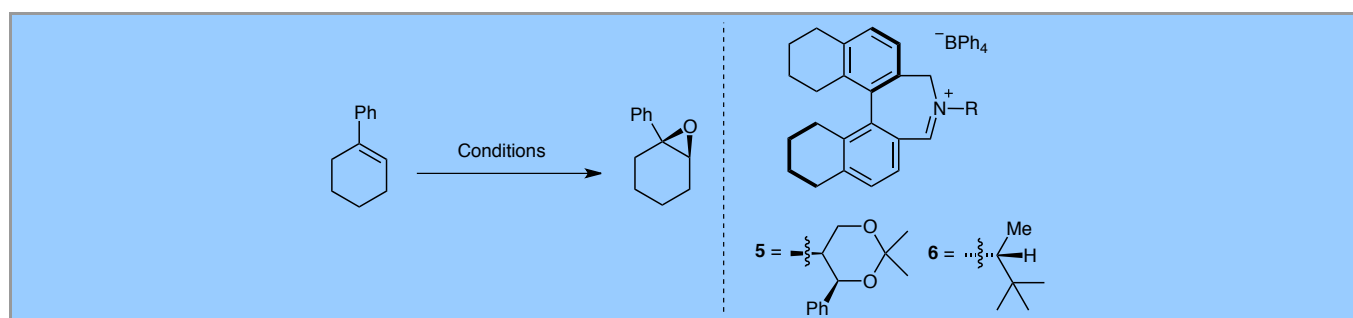| Entry	Conditions	Time (h)	Conv. (%)[a]	ee (%)[b]	ref
1	Iminium salt **4** (10 mol%), X = BPh$_4$, Oxone (2.0 equiv.), Na$_2$CO$_3$ (2.0 equiv.), MeCN/H$_2$O (1:1), 0 ºC	0.30	100	60	1(a)
2	Iminium salt **4** (5 mol%) X = TRISPHAT, Oxone (1.0 equiv.), NaHCO$_3$ (4.0 equiv.), 18-C-6 (2.5 mol%), CH$_2$Cl$_2$/H$_2$O (3:2), 0 ºC.	3.0	90	69	2(q)
3	Iminium salt **4** (10 mol%), X = BPh$_4$, TPPP (2.0 equiv.), MeCN, 0 ºC	0.03	100	58	6
4	Iminium salt **4** (10 mol%), X = BPh$_4$, H$_2$O$_2$ (50%, 6.0 equiv.), NaHCO$_3$ (0.2 equiv), MeCN:H$_2$O (9:1), 0 ºC.	24	48	36	10
5	Iminium salt **4** (10 mol%), X = BPh$_4$, sodium hypochlorite (6.0 equiv.), K$_2$CO$_3$ (0.25 equiv), MeCN, 0 ºC.	24	100	55	11
6	Iminium salt **4** (5 mol%), X = BPh$_4$, H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (5.0 mol%), MeCN, 0 ºC.	0.30	100	50	This work
7	Iminium salt **4** (5 mol%), X = BPh$_4$, H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (1.0 mol%), MeCN, 0 ºC.	0.35	100	47	This work
8	H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (1.0 mol%), MeCN, 0 ºC.	24	<5	–	This work

[a] Conversion evaluated by comparison of the alkene vs epoxide CH signals in the ^{1}H NMR spectrum; [b] ee determined by Chiral GC[c] ee determined by ^{1}H NMR spectroscopy in CDCl$_3$ using [(+)-Eu(hfc)$_3$] as the chiral shift reagent and tetramethylsilane as the internal standard

Both systems suffer from reduced rates of reaction and lower ees when compared to the original oxone-mediated processes. We were intrigued by the report of Du Bois regarding the use of a diarylselenide and hydrogen peroxide as a stoicheiometric oxidant for oxaziridine-mediated catalysis (Scheme 4).[12] However, this system required the use of the bis(3,5-bis(trifluoromethyl)phenyl) diselenide (ArSe$_2$), which is not commercially available and must be prepared using the procedure reported by ten Brink.[13] The optimized system also employs urea-hydrogen peroxide as oxidant (water must to be excluded from this process to prevent hydrolysis of the parent imine).
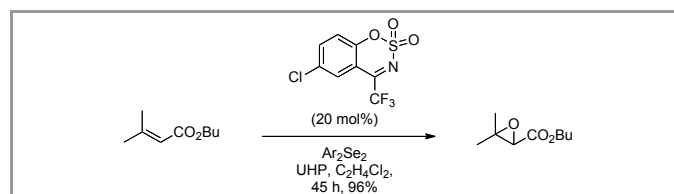
Scheme 4 Du Bois' oxaziridine catalysed oxidation

We began our studies using commercially available diphenyldiselenide (5 mol%) and aqueous hydrogen peroxide (50%, 3.0 equiv.) in combination with our iminium salt catalysts, and were delighted to find that under these simple conditions rapid conversion of 1-phenylcyclohexene to epoxide was observed when using catalyst **4**. Reducing the loading of diphenyldiselenide to 1 mol% appeared to have little effect on the rate of reaction, and this appears to be comparable to that of the aqueous oxone system. Table 1 provides a comparison of various sets of reaction conditions drawn from our own work and that of others. It can be seen

Table 2 Highly enantioselective epoxidation of 1-phenylcyclohexene using catalysts **5** or **6**
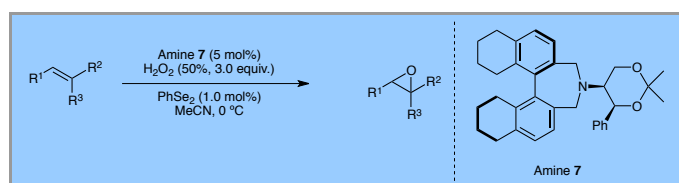

Entry	Conditions	Catalyst	Time (h)	Conv. (%)[a]	ee (%)[b]
1	Iminium salt **5** (5 mol%), X = BPh$_4$, Oxone (2.0 equiv.), Na$_2$CO$_3$ (2.0 equiv.), MeCN/H$_2$O (1:1), 0 ºC	**3**	2	75	88[c]
2	Iminium salt **5** (5 mol%), X = BPh$_4$, H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (1.0 mol%), MeCN, 0 ºC.	**3**	2	76	85
3	Iminium salt **6** (5 mol%) X = BPh$_4$, Oxone (1.0 equiv.), NaHCO$_3$ (4.0 equiv.), 18-C-6 (2.5 mol%), CH$_2$Cl$_2$/H$_2$O (3:2), 0 ºC.	**4**	4	76	85
4	Iminium salt **6** (5 mol%), X = BPh$_4$, H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (1.0 mol%), MeCN, 0 ºC.	**4**	2	70	85

[a] Conversion evaluated by comparison of the alkene vs epoxide CH signals in the ^{1}H NMR spectrum; [b] ee determined by Chiral GC[c] ee determined by ^{1}H NMR spectroscopy in CDCl$_3$ using [(+)-Eu(hfc)^3] as the chiral shift reagent and tetramethylsilane as the internal standard

that this new system is just as active as that reported using oxone, and the level of enantioselectivity is similar, suggesting that background oxidation of the alkene substrate by the selenium oxidant does not occur.

In order to develop a more highly enantioselectve approach for epoxidation of unfunctionalized alkenes, we opted to employ the iminium salt catalysts **5**[14] and **6**.[2w] Again, the use of the diphenyldiselenide system compares well with the standard oxone conditions, with similar isolated yields and almost identical levels of enantioselectivity (Table 2).[15]

Very few reports have emerged of the amine-catalysed epoxidation of alkenes. Aggarwal in 2003[16] and Yang in 2005[17] independently reported employing oxone and a secondary amine, although both we and Lacour have shown that amines related to **7**[14] catalyse the epoxidation of unfunctional alkenes.[18] In these reactions, unlike those reported by Aggarwal and Yang, which are believed to occur through hydrogen bonding to persulfate, oxone

2	(structure: Cl-C6H4 C=CH2 C6H4-Cl)	0.9	97	80
3	(structure: F-C6H4 C=CH2 C6H4-F)	1.5	98	86

[a] Amine **7** (5 mol%), H$_2$O$_2$ (50%, 3.0 equiv.), PhSe$_2$ (1.0 mol%), MeCN, 0 ºC; [b] Conversion evaluated by comparison of the alkene vs epoxide CH signals in the ^{1}H NMR spectrum.

converts the amines firstly to the iminium and subsequently to the oxaziridinium ions, thus enabling epoxidation to proceed.

We were interested to discover if this was also possible using the diphenyldiselenide/hydrogen peroxide system. Thus, amine **7** was subjected to the conditions outlined in Table 3. Excellent yields and enantioselectivities were obtained and were almost identical to those observed using the corresponding iminium salt.

A plausible dual catalytic cycle is outlined in scheme 5: benzeneperseleninic acid[19] generated from hydrogen peroxide in turn oxidizes the iminium ion, thus generating the oxaziridinium ion required for enantioselective oxygen transfer to the alkene. The benzeneseleninic acid by-product is then reoxidized to the active oxidant by hydrogen peroxide.

Table 3 Highly enantioselective epoxidation of substrates using amine **7** as precatalyst[a]

Amine **7**

Entry	Substrate	Time (h)	Conv. (%)[b]	Ee (%)
1	(structure: Ph-cyclohexene)	4 (2)	76 (76)	85 (88)
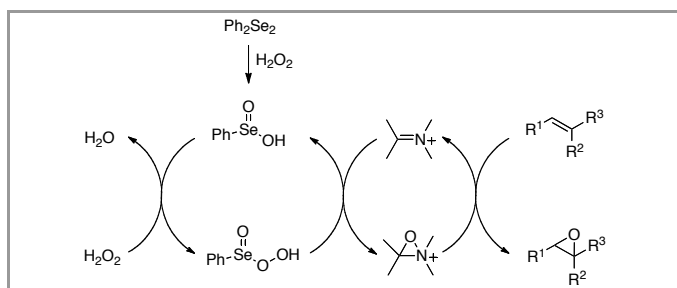
Scheme 4 A plausible dual catalytic cycle

In conclusion we have demonstrated for the first time that perseleninic acid derived *in situ* from diphenyldiselenide and hydrogen peroxide is a useful oxidant system for oxaziridinium salt-catalysed epoxidation. The reaction rates and ees are similar to those observed when oxone is used as a stoicheiometric oxidant, but this system benefits from a simple work up and no inorganic waste products, offering an attractive alternative to more standard approaches.

Acknowledgment

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(14)   2,2'-*bis*-(Bromomethyl)-octahydrobinaphthalene was prepared according to the method of Ruan.[20] The dibromide (0.20 g, 0.45 mmol) and (*S,S*)-acetonamine (0.20 g, 0.45 mmol) were dissolved in acetonitrile (30 mL) and potassium carbonate (0.185 g, 1.34 mmol) added. The solution was stirred with heating under reflux for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (30 mL), washed with water (2 x 30 mL), dried (MgSO$_4$), filtered and solvents removed under reduced pressure to afford **7** as a colourless solid (0.20 g, 91%); m.p. 170-171 ºC; $[\alpha]^{20}_D - 8.4$ (c 0.9, CH$_2$Cl$_2$); Found: C, 82.52; H, 7.66; N, 2.92; C$_{34}$H$_{39}$NO$_2$ requires C, 82.72; H, 7.96; N, 2.84 %; ν$_{max}$ (film)/cm-1 3052, 2932, 1633, 1599, 1449, 1443, 1388, 1300, 1200, 1142, 1109, 950, 850, 731; ^{1}H NMR (400MHz, CDCl$_3$): δ$_H$ 1.59 (3 H, s,), 1.64 (3 H, s), 1.74-1.78 (8 H, m), 2.12-2.19 (2 H, m), 2.62-2.65 (3 H, m), 2.85 (4 H, t, J 6.8 Hz), 3.10 (2 H, d, J 12.4 Hz), 3.50 (2 H, d, J 12.0 Hz), 4.11-4.23 (3 H, m), 6.90 (2 H, d, J 7.2 Hz), 6.99 (2 H, d, J 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ$_C$ 19.2, 22.7, 22.8, 23.0, 23.1, 27.6, 27.7, 29.5, 29.6, 52.8, 59.9, 61.3, 125.9, 126.7, 127.6, 128.0, 132.3, 133.5, 154.9, 137.8, 158.1, 138.7; m/z (ESI) 494.3043; C$_{34}$H$_{40}$NO$_2$ [M$^+$H] requires 494.3059. Compound **7** (0.08 g, 0.16 mmol) was dissolved in dichloromethane (20 mL) and *N*-bromosuccinimide (0.04 g, 0.19 mmol, 1.2 eq.) added. The solution was heated under reflux for 4 h. After cooling to room temperature, the sol-

vent was removed under reduced pressure. The residue was dissolved in ethanol, and sodium tetraphenylborate (0.06 g, 0.018 mmol, 1.1 eq.), dissolved in the minimum amount of acetonitrile, was added in one portion, and the reaction mixture stirred for 5 min. The solvents were removed under reduced pressure to give a yellow residue that was recrystallized from hot ethanol to give **5** as a yellow crystalline solid, washed with cold ethanol and diethyl ether (0.10 g, 76%), m.p. 130-135 °C; $[\alpha]^{20}_D$ − 10.0 (c 0.8, CH$_2$Cl$_2$); Found: C, 85.45; H, 6.82 ; N 1.63. C$_{58}$H$_{58}$BNO$_2$ requires C, 85.80; H, 7.20; N, 1.73 %; ν_{max} (film)/cm^{-1} 3053, 2936, 1619, 1575, 1488, 1427, 1382, 1202, 1111, 838, 733, 703; ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.55-1.62 (6 H, d), 1.76-2.27 (12 H, m), 2.53-2.99 (6 H, m), 3.45-3.71(3 H, m), 5.00-5.05 (1 H, m), 6.73-6.78 (4 H, m), 6.84- 7.11 (10 H, m), 7.20-7.28 (8 H, m), 7-29-7.36 (8 H, m) ppm; ^{13}C NMR (100 MHz, CDCl$_3$); δ_C (mixture of rotamers) 14.2, 18.8, 18.9, 21.0, 21.8, 22.1, 22.2, 22.5, 22.8, 22.9, 23.3, 26.8, 27.8, 27.95, 28.02, 29.5, 29.6, 29.7, 29.6, 29.7, 30.2, 30.6, 30.9, 48.4, 54.8, 55.2, 60.4, 60.5, 63.2, 66.4, 71.7, 73.8, 99.1, 100.4, 122.3, 124.1, 124.7, 124.8, 125.1, 125.4, 125.8, 125.8, 125.9, 127.1, 128.0, 128.2, 128.4, 128.6, 128.8, 128.9, 129.0, 129.7, 130.5, 131.7, 133.8, 134.1, 134.6, 134.9, 135.2, 135.6, 135.8, 136.0, 136.1, 137.7, 138.8, 139.8, 140.4, 140.5, 144.0, 144.6, 146.3,187.0; m/z (EI) 492.2897; C$_{34}$H$_{38}$NO$_2$ [M$^+$, cation] requires 492.2895.

(15) **General procedure for epoxidation using diphenyldiselenide, hydrogen peroxide and iminium salt or amine:** The alkene (1.0 equiv.) was dissolved in acetonitrile (2 mL per mmol alkene), the iminium salt (or amine) catalyst (5 mol %) was added along with diphenyldiselenide (1 mol%). The reaction vessel was cooled in an ice bath for 5 minutes before hydrogen peroxide (50%, 3.0 equiv.) was added dropwise over 5 minutes. The reaction progress was followed using thin-layer chromatography and when the reaction was complete, diethyl ether (20 mL) was added. The mixture was washed twice with water and once with saturated brine and dried over MgSO$_4$. The solvents were removed under reduced pressure and the crude product was purified using column chromatography on silica gel (ethyl acetate/petroleum ether/triethylamine).

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Graphical Abstract:
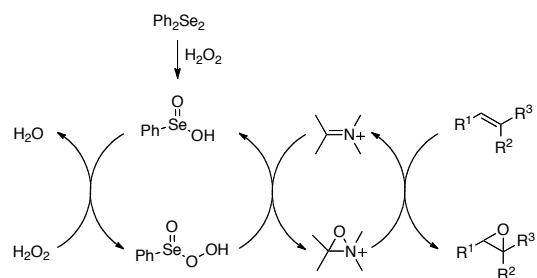
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